# PATENT COOPERATION TREATY



**PCT**

From the:
INTERNATIONAL SEARCHING AUTHORITY

To:

A.P.T. Patent and Trade Mark Attorneys
PO Box 222
MITCHAM SA 5062

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| | Date of mailing *(day/month/year)* 19 MAY 2005 |
| Applicant's or agent's file reference<br>2859pct | **FOR FURTHER ACTION**<br>See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| **PCT/AU2005/000461** | 31 March 2005 | 31 March 2004 |

International Patent Classification (IPC) or both national classification and IPC
**Int. Cl.** [7] G01N 33/50 G01N 33/92

Applicant
CHILDREN, YOUTH AND WOMEN'S HEALTH SERVICE et al

1. This opinion contains indications relating to the following items:

- [X] Box No. I — Basis of the opinion
- [ ] Box No. II — Priority
- [ ] Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV — Lack of unity of invention
- [X] Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI — Certain documents cited
- [ ] Box No. VII — Certain defects in the international application
- [X] Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.

**PCT/AU2005/000461**

**Box No. I Basis of the opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.

**PCT/AU2005/000461**

**Box No. V** **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---|---|---|
| Novelty (N) | Claims **3, 22** | **YES** |
| | Claims **1, 2, 4-21 & 23-27** | **NO** |
| Inventive step (IS) | Claims **22** | **YES** |
| | Claims **1-21, 23-27** | **NO** |
| Industrial applicability (IA) | Claims **1-27** | **YES** |
| | Claims **none** | **NO** |

2. Citations and explanations:

The following citations are considered to be relevant:

D1= Whitfield PD *et al* (2002) *Mol. Gen & Metabolism* **75**: 46-55
D2 = Cable WJL *et al* (1982) *Neurology* (Ny) **32**: 1139-1145
D3= Fujiwaki T *et al* (2002) *Brain & Development* **24**:170-173
D4= Fujiwaki T *et al* (2002) *J. Chromatography B* **776**: 115-123
D5= Oshima M *et al* (1990) *Bioch et Biophys Acta* **1043**: 157-160

D1 discloses the relationship among genotype, glycolipid substrates and the clinical manifestations of a Lysosomal storage disease: Gaucher disease. Plasma glycolipids were analysed using electrospray ionization-tandem mass spectrometry. Patients with Gaucher disease were found to have an increased ratio between two glycolipids: 16:0-glucosylceramide/16:0-lactosylceramide ratio, thus uncovering a correlation between genotype and phenotype (abstract, Figure 1 and Figure 3).
As such D1 renders claims 2 and 4-16 to be neither novel nor inventive.

The difference between D1 and the present application is that methods for assessing LSD status of individuals by measuring the level of at least three lipid containing indicator compounds. However once D1 demonstrated that the ratio between two indicator compounds could be used to assess the LSD status of individuals, for a person skilled in the art to use three or more indicator compounds to calculate the LSD ratio is an obvious step, not requiring any inventiveness and attainable by routine steps alone. As such in light of D1 claims 1 and 23 – 27 are not inventive.

D2 discloses the detection of heterozygotes for Fabry disease, an LSD, by examining glycolipids in urinary sediment by HPLC. The total glycolipid fraction was increased 10 to 100 fold in heterozygotes and trihexosyl ceramide (CTH) was 2 to 70 fold times the normal range, with digalactosyl ceramide (Digal-Cer) also increased (Abstract and Table page 1143) . The ratio CTH and DigalCer over hydroxyfattyacid glucosyl ceramide was increased and appears to be characteristic of Fabry disease. As such D2 renders claims 1, 2, 4-8, 11-14, 16, 17 and 19 to be neither novel nor inventive.

The difference between D2 and the present application is that the ratio is selected from a 1st group comprising Cer, LC or CTH and a 2nd group comprising SM as well as methods in which the indicator compounds are C24:0 or C24:1 . However once D2 discloses that the ratio between two components of the CTH and DigalCer over hydroxyfattyacid glucosyl ceramide was increased in Fabry disease it is obvious for a person skilled in the art to substitute the indicator compounds for others and calculate the LSD ratio. As such in light of D2 the following claims are not inventive: claims 18, 20 and 21.

(continues supplemental page)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International application No.

**PCT/AU2005/000461**

**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 12 is not clear. It appears that it refers to the method as in claim 4 wherein the *sample* is whole blood. However the word sample was omitted.

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

International Application No.

**PCT/AU2005/000461**

**Supplemental Box**

**In case the space in any of the preceding boxes is not sufficient.**

Continuation of: **Box V**

D3 discloses the measurement of sphingolipids using delayed extraction matrix-assisted laser desorption ionization time-of –flight mass spectrometry (DE MALDI-TOF-MS) from cultured fibroblasts from patients with 4 LSDs one being Gaucher Disease. In GD patients the ratio glucosylceramide/sphingomyelin was increased while fibroblasts of patients suffering from another LSD, Farber Disease, displayed high ratios of ceramide/sphingomyelin and ceramide/monohexosylceramide (Abstract and Figure 2). Thus D3 renders claims 2, 4-9, 11 and 13-16 to be neither novel nor inventive.

The difference between D3 and the present application is that methods for assessing LSD status of individuals by measuring the level of at least three lipid containing indicator compounds. However once D3 demonstrated that the ratio between two indicator compounds could be used to assess the LSD status of individuals, for a person skilled in the art to use three or more indicator compounds to calculate the LSD ratio is an obvious step, not requiring any inventiveness and attainable by routine steps alone. As such in light of D1 claims 1 and 23 – 27 are not inventive.

D3 also discloses that a number of lipid containing indicator compounds may be analysed and their ratios may indicate which of the LSDs is the one carried by the patient. Thus in light of D3 it would be obvious for a person skilled in the art to screen an individual for two or more LSDs by taking a single sample and estimating the level of three or more lipid-containing indicator compounds and estimating LSDs' ratios. Thus in view of D3 claim 3 is not inventive.

D4 discloses the application of DE MALDI-TOF-MS for the analysis of sphingolipids obtained form serum samples of two patients with Gaucher disease. The GD patients have ceramide monohexoside/sphingomyelin ratio increased compared with the controls. As such D4 renders claims 2, 4-9 and 11-16 to be neither novel nor inventive.

Using the same reasoning as for D3, D4 renders claims 1 and 23-27 to be not inventive.

D5 discloses the isolation and analysis by HPLC of neutral phospholipids from urinary sediment of six patients with Fabry's disease and of 11 members of their family. In Table I the molar ratios of Ceramide monohexoside over lactosylceramide plus galactobiosyl ceramide CDH/CMH indicate that the molar ratio in patient was higher in patients than in controls. This study was alos able to identify Fabry heterozygotes even though these showed no clinical signs. As such D5 renders the following claims to be neither novel nor inventive: claim 2, 4-8, 11, 13 and 14.

The difference between D5 and the present application is that the ratio is selected from a 1st group comprising Cer, LC or CTH and a 2nd group comprising SM as well as methods in which the indicator compounds are C24:0 or C24:1 . However once D5 discloses that ratio of Ceramide monohexoside over lactosylceramide plus galactobiosyl ceramide CDH/CMH in Fabry disease patients was higher than in controls it is obvious for a person skilled in the art to substitute the indicator compounds for others and calculate the LSD ratio. As such in light of D5 the following claims are not inventive: claims 1 and 17-21.

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